Remarks

Claims 47 and 60-73 are pending in the subject application. By this Amendment, Applicants have provided a substitute specification. Claims 1-46, 48-63 and 69-73 are canceled, claims 47 and 68 are amended, and claims 74-96 are newly added. Support for the new and amended claims can be found throughout the subject specification and in the claims as originally filed (see, for example, page 10, lines 17-26; page 13, lines 8-31; page 15, lines 15-30; and Example 1, pages 27-48). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 47, 64-68 and 74-96 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested. All reference to page and line numbers in this response relate to the substitute specification concurrently filed herewith.

As an initial matter, Applicants gratefully acknowledge the Examiner's indication that Applicant should amend the first line of the specification to reflect the relationship between the instant application and application serial number 09/440,514 (filed November 15, 1999). Applicants note that this information was previously provided to the Examiner in a Preliminary Amendment dated May 19, 2003. For the convenience of the Examiner, a copy of this amendment is attached hereto and its entry is respectfully requested.

In addition, Applicants gratefully acknowledge the Examiner's indication that page 4, line 20, page 24, lines 12-27 and Figures 7B and 7C of the disclosure should be amended to correct typographical errors. By this Amendment, a substitute specification and new Figures 7B and 7C are being provided to correct these errors and a number of other typographical errors found throughout the specification. The undersigned avers that the substitute specification and replacement Figures contain no new matter. Entry of the new Figures and specification are respectfully requested. A red-lined copy of the specification indicating the changes made therein is also enclosed.

Claims 68 and 73 are rejected under 35 US §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully submit that antibodies having the binding specificity of AZ20, A76, and Z25 can be reproducibly obtained following the teachings of the specification. For example, the specification clearly teaches methods of making and screening both polyclonal and monoclonal antibodies (e.g.,

substitute specification at pages 26-32 and page 42). However, in the interest of advancing prosecution in this matter the undersigned has provided a declaration in this matter indicating that the AZ20 hybridoma has been deposited under the terms of the Budapest Treaty at the Collection Nationale de Cultures de Microorganisms, Institute Pasteur (CNCM), 25 rue de Docteur Roux, F-76724, Paris Cedex 15, France on November 8, 2000 and given CNCM Registration Number I-2576. This information has also been inserted into the specification (see substitute specification page 22, lines 24-28). Furthermore, all restrictions on this hybridoma will be irrevocably and without restriction or condition removed at the time a patent issues in this matter. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claim 47 and 60-73 are rejected under 35 US §112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Particularly, the Office Action argues that the specification is enabling only for a method of stimulating the cytotoxicity of NK cells with antibodies of human origin or a polyclonal, monoclonal, or humanized antibody that specifically binds to a polypeptide comprising SEQ ID NO: 2 or a peptide consisting of SEQ ID NOs: 4 or 7. The Office Action continues, arguing that the specification fails to enable: 1) methods of stimulating the cytotoxicity of NK cells with any antibody, or antibody binding fragment thereof, of human origin or a polyclonal, monoclonal, or humanized antibody that specifically binds to a polypeptide "having at least" an amino acid sequence of SEQ ID NOs: 2-7 wherein the antibody or fragment thereof is coupled to a label (e.g., a fluorescent label or a solid substrate such as a microspheres, hollow fibers, or dense particles). The Office Action then cites to *In re Wands* (858 F2d 731, 737; 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and lists several factors that are indicated to be most relevant to this rejection. These factors include: 1) the scope of the claim; 2) the amount of guidance or direction provided; 3) the lack or sufficient working examples; 4) the unpredictability in the art; and the amount of experimentation required to enable one skilled in the art to practice the claimed invention. The Office Action further argues that claims 47 and 60-73 fail to comply with the written description requirement of 35 U.S.C. § 112, first paragraph on the grounds that the specification fails to provide adequate written description about the structure associated with the function of any polypeptide that contains additional undisclosed amino acids. Applicants traverse.

In view of the amendments made to the instant claims, it is respectfully submitted that many of the issues raised in the Office Action are now moot. However, Applicants traverse the rejection as applied to polypeptides comprising SEQ ID NO: 4 or 7 for methods of stimulating the cytotoxicity of NK cells.

As the Patent Office will note, the claims recite "A method for stimulation of cytotoxicity by NK cells, comprising: contacting said NK cells with an amount of antibody effective to stimulate the activity of said NK cells, said antibody specifically binding to a polypeptide comprising the amino acid sequence of: SEQ ID NO:2; SEQ ID NO: 4; or SEQ ID NO: 7." Thus, the scope of the claim indicates that the antibodies that are contacted with the NK cells specifically bind to SEQ ID NO: 2 or subsequences thereof (SEQ ID NOs: 4 or 7). The Patent Office further argues that the specification provides insufficient guidance with respect to the structure of any polypeptide to which an antibody binds and that given the indefinite number of undisclosed polypeptides, it is unpredictable which polypeptide is useful for making antibodies effective for the stimulation of NK activity. The Office Action goes on to cite a number of references in support of its assertion regarding the enablement of the subject application. The Office Action also argues that it is there is inadequate written description with respect to the structure of those polypeptides encompassed within the scope of the currently pending claims. It is respectfully submitted that the scope of such a claim is supported by the as-filed specification (*i.e.*, having adequate written description with respect to the claimed method and enabling the practice of the claimed invention) since it is taught that antibodies that specifically bind to SEQ ID NOs: 2 (the full length human NK p30 polypeptide), 4 (the extracellular domain of human NK p30), or 7 (an antigenic fragment of human NK p30). Indeed, polyclonal antibodies that were generated against the polypeptide of SEQ ID NO: 7 conjugated to KLH (an exemplary polypeptide comprising SEQ ID NO: 7 [see substitute specification page 33, lines 5-20]) are able to bind to and/or stimulate the cytotoxic activity of the NK cells (see Example 1). As the Patent Office will note, polyclonal antibodies were generated against SEQ ID NO: 7 which was conjugated to KLH specifically bound to NKp30 polypeptides. Furthermore, these polyclonal antibodies were able to immunoprecipitate polyclonal NK cell populations (see, for example, Figure 9 and pages 32-33 and 44-45 of the substitute specification). It is further submitted that adequate written description exists for polypeptides comprising SEQ ID

NO: 4 or 7 in that the "function" associated with these polypeptides is the binding of antibodies generated against these peptide fragments of SEQ ID NO: 2 or against the full-length sequence of SEQ ID NO: 2. Indeed, it is respectfully submitted that one skilled in the art would reasonably expect antibodies directed against SEQ ID NOs: 2, 4, or 7 to specifically bind to the NKp30 polypeptide and stimulate the cytotoxic activity of NK cells given the evidence provided in the as-filed application in Example 1 (namely that such antibodies immunoreact with the NKp30 polypeptide that is expressed on the surface of NK cells (see, for example Figures 3-7 and Figures 9A-B and the descriptions thereof at pages 22-27).

Applicants, further, respectfully submit that the specification, as filed, enables the breadth of the presently claimed invention. As the Patent Office is aware, the quantity of experimentation can be "considerable", "tedious", "laborious", and "time-consuming" as long as the experiments are merely "routine". See *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (B.P.A.I. 1982) ("[t]he test [of enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine."); *Ex parte Erlich* 3 U.S.P.Q.2d 1011 (B.P.A.I. 1982) (observing that although a method might be "tedious and laborious," such experimentation is nevertheless "routine" defining "routine" experiments as those which use known methods in combination with the variables taught in the patent to achieve the expected, specific, patented result). In the case of the instant invention, Applicants submit that the specification provides explicit teachings regarding methods of making antibodies that stimulate the cytotoxicity of NK cells, methods of assaying NK cells to identify such antibodies, (substitute specification at pages 27-32) as well the criteria by which stimulatory antibodies according to the subject invention are identified (see substitute specification at pages 9-10, 27-32, Example 1, and Example 2 (pages 48-50)). Accordingly, reconsideration and withdrawal of the rejections is respectfully requested.

Previously presented claim 72 was rejected as constituting new matter in the previous Office Action. While this claim has been cancelled, additional new claims (see new claim 94) reciting this limitation have been presented in this response. Applicants submit that these claims are supported in the originally filed specification at, for example, page 10, about line 20 or pages 50-51 (Example 3) of the substitute specification. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 47, 60-63, 69-70, 72 and 73 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. It is respectfully submitted that these rejections are moot in view of the amendments made to the claims and withdrawal of the rejection is respectfully requested. Accordingly, reconsideration and withdrawal of the rejection under 35 US §112, second paragraph, is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: 2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

FCE/ssa

Enclosures: Substitute specification
Red-lined copy of specification
Replacement Figures 7B and 7C
Copy of Preliminary Amendment dated May 19, 2003
Declaration with attached copy of CNCM registration for deposit of hybridoma AZ20 under Budapest Treaty